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(54) **GAMBOGIC ACID DERIVATIVES, PREPARATIVE METHODS AND USES THEREOF**

GAMBOGINSÄUREDERIVATE, VERFAHREN ZU IHRER HERSTELLUNG UND VERWENDUNGEN DAVON

DÉRIVÉS DE L'ACIDE GAMBOGIQUE, PROCÉDÉS DE PRÉPARATION ET UTILISATIONS DE CEUX-CI

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(Cont. next page)

- **KUEMMERLE J ET AL: "Synthesis of caged 2,3,3a,7a-tetrahydro-3,6-methanobenzofuran -7 (6H)-ones: Evaluating the minimum structure for apoptosis induction by gambogic acid", BIOORGANIC & MEDICINAL CHEMISTRY, PERGAMON, GB, vol. 16, no. 8, 15 April 2008 (2008-04-15) , pages 4233-4241, XP022617873, ISSN: 0968-0896, DOI: 10.1016/J.BMC. 2008.02.084 [retrieved on 2008-02-29]**
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Remarks:

The file contains technical information submitted after the application was filed and not included in this specification

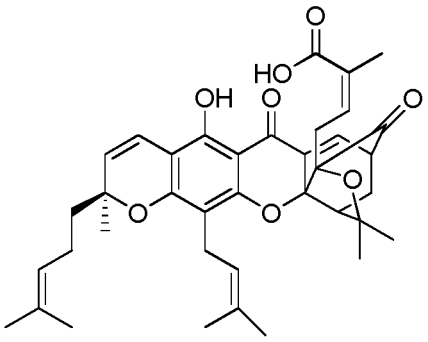
Description

Field of the invention

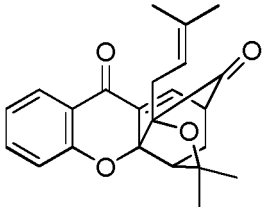
[0001] The present invention relates to a field of pharmaceutical chemistry, more specifically, the present invention relates to a garcinia derivative, its preparing method, and medicinal use. The derivative of the present invention is a structurally simplified analogue of the gambogic acid compound which possesses anti-cancer characteristics and could be used for the preparation of anti-tumor drugs.

Background of the invention

[0002] It has been recently discovered that the natural product gambogic acid that is extracted from the gambogic resin of the Garcinia plant,is an effective ingredient in terms of anti-tumor characteristics. Research has shown that gambogic acid could selectively kill the various tumor cells without influencing the human hematopoietic or immune system. The gambogic acid could also combine with various proteins which are related to tumor formation and invasion, and thus induce apoptosis of the tumor cells. Therefore the gambogic acid could be used as an effective apoptosis inducer for various tumor systems. The formula of gambogic acid is shown below:



Formula of Gambogic Acid



Compound (II)

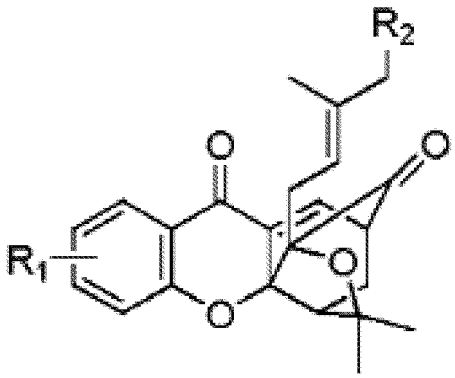
[0003] Due to the fact that the molecular weight of gambogic acid is relatively high, the presence of a corresponding group in modified structure might lead to undesired druggability, furthermore, the gambogic acid is obtained from natural products via extraction and separation, which does not facilitate industrial production. A structurally simplified analogue of the gambogic acid has been reported (Compound (II)), however, the anti-pharmaceutical test of the structurally simplified analogue of the gambogic acid (Compound (II)) showed that its anti-tumor activity is significantly reduced compared to the gambogic acid, thereby leading to poor medicinal properties. (Bioorganic & Medicinal Chemistry 16 (2008) pgs. 4233 - 4241).

[0004] WO2008/057604 discloses gambogic acid derivatives with anti-proliferative activity.

Summary of the invention

[0005] In the present invention, the structurally simplified analogue which is based on the gambogic acid caged scaffold structure, is prepared for the first time by using a tactic of precursor compound structural simplification. The compound of the present invention possesses similar anti-tumor activity when compared with that of gambogic acid, and it could be used for the preparation of anti-tumor drugs.

[0006] The compound structure of the present invention is shown in Formula (I):



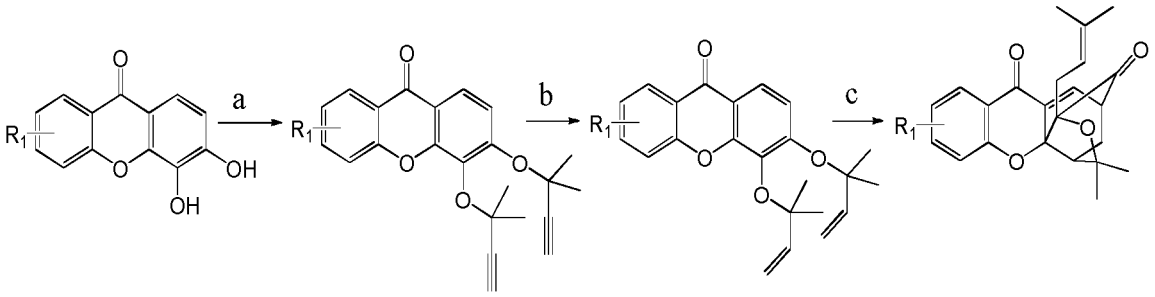
Formula (I)

wherein said compound of Formula (I) carries one or two R1; when it carries one R1, R1 is a hydroxyl group; when it carries two R1, one of R1 is a hydroxyl group, and the other R1 is an isopentenyl group;

wherein R2 is hydrogen, halogen, a hydroxyl group, an alkoxy group containing C1 - C4 carbons, an amide group containing C1 - C4 carbons, a carboxyl group, or an aldehyde group.

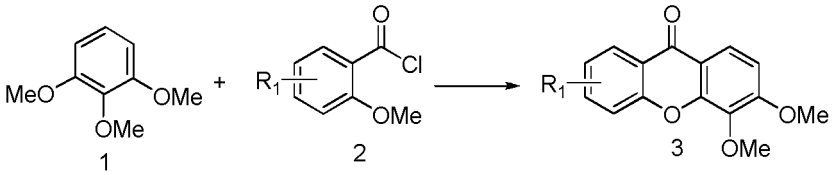
[0007] The preferred R2 is hydrogen, a hydroxyl group, an aldehyde group, a carboxyl group, or an amide group.

[0008] The compound of the present invention is prepared via the following methods, wherein the reaction formula is:

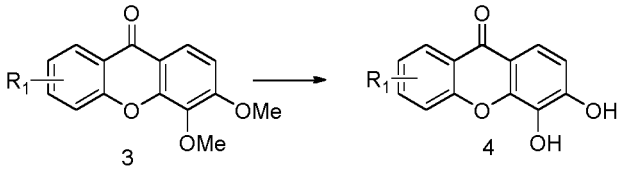


wherein the included reagents and conditions are as follows: a. K_2CO_3, KI, chloro-methyl-butyne, CuI and acetone; b. 10% $Pd/BaSO_4$, ethyl acetate; and c. DMF (N, N-dimethyl formamide).

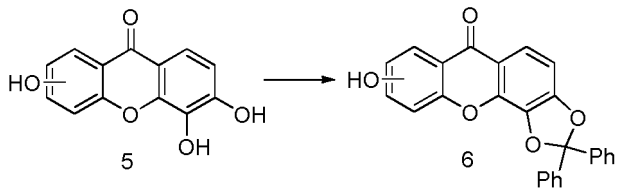
[0009] Take the compound wherein R_1 is a hydroxyl group and R_2 is a hydrogen as an example, the said compound could be used as reference for the other substituent, the more detailed and preferred preparing method is shown as below:



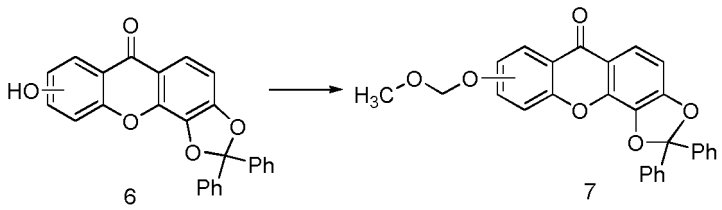
[0010] The compound 3 is obtained from compound 1 and compound 2 via a two-step reaction. The compound 1 and compound 2 react for 12 - 18 hours at room temperature. The preferred solvent is ethylether and $AlCl_3$ is added to the reaction solution. After the reaction, the obtained product without any treatment is directly heated to reflux and is then reacted for 20 - 30 hours in the strong alkali. As a result, the compound 3 is obtained. The preferred solvents are water and methanol; the ratio between said water and methanol is 1:1 to 4:1; and inorganic alkali, for instance, NaOH, KOH, and the like is then added to the reaction solution.



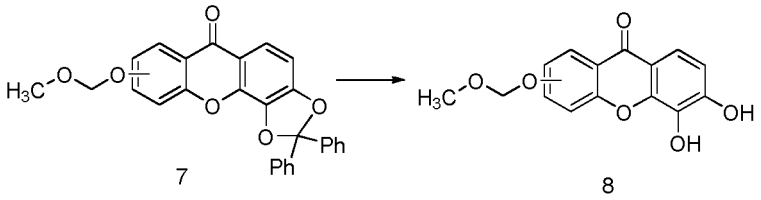
[0011] The compound 3 is heated and refluxed for 6 hours in a mixed solution containing 40% HBr and glacial acetic acid, as a result, the compound 4 is obtained. The solvent ratio between glacial acetic acid: 40% HBr is 1:1 to 4:1.



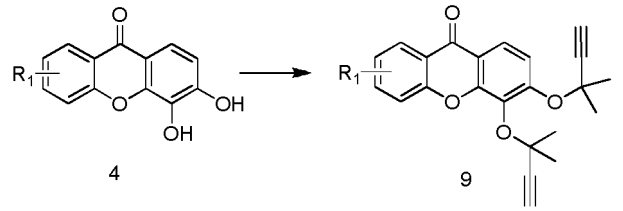
[0012] When R_1 is hydroxyl group, the compound 6 is obtained via reaction between the compound 5 and diphenyl dichloromethane, wherein the preferred solvent is xylene or diphenylether and the preferred reaction temperature is 160°C - 180 °C.



[0013] The compound 6 reacts with chloromethyl methyl ether at room temperature, and as a result, the compound 7 is obtained. The solvent is selected from acetonitrile, N,N-dimethyl formamide (DMF), acetone, dichloromethane, and the like; the reaction time is 6 - 10 hours; and the inorganic alkali or organic alkali, for instance, NaOH, KOH, K_2CO_3, triethylamine, and the like could be added during the reaction.

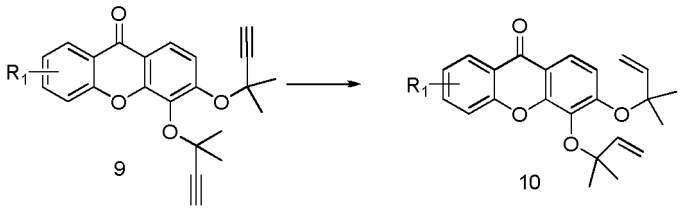


[0014] The compound 8 is obtained via hydrogenation of the compound 7 at normal pressure, wherein the reaction temperature is 20°C - 50°C; the solvent is selected from THF, acetonitrile, DMF, methanol, trichloromethane, and the like; and a hydrogenation catalyst should also be added, for instance, 5% Pd/C, 10% Pd/C, and the like.

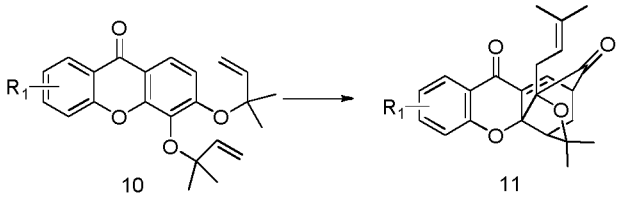


[0015] When R_1 is the other substituent or chloromethyl methyl, except said hydroxyl group, the compound 9 is obtained via reaction between the compound 4 and chloro-methy l-butyne, wherein the reaction temperature is 60°C - 90°C, and the solvent is selected from DMF, acetone, acetonitrile, dichloromethane, trichloromethane, and the like. The inorganic

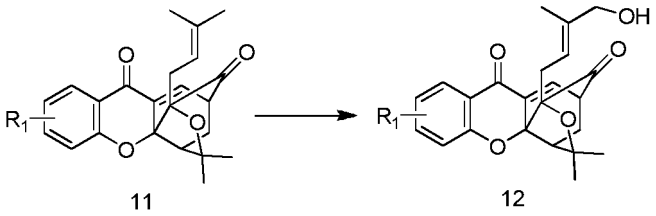
alkali or organic alkali, for instance, NaOH, KOH, K_2CO_3, triethylamine, and the like should also be added to the reaction, furthermore, the catalyst CuCl, CuI, or KI should also be added.



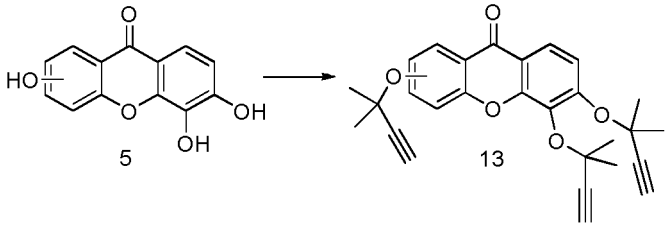
[0016] The compound 10 is formed via hydrogenation of the compound 9 at normal pressure, wherein the reaction temperature is 20°C - 50°C; the solvent is selected from ethyl acetate, THF, acetonitrile, ethanol, and the like; a hydrogenation catalyst, for instance, 5% Pd/C, 10% Pd/C, 5% Pd-$BaSO_4$, 10% Pd-$BaSO_4$, and the like, should also be added.



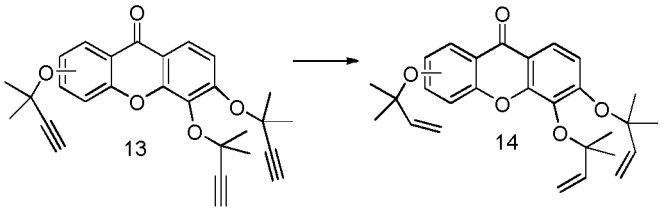
[0017] The compound 10 is heated to be rearranged, and as a result, the compound 11 is obtained, wherein the reaction temperature is 120°C - 180°C, and the solvent is selected from toluene, DMF, diphenyl ether, and the like.



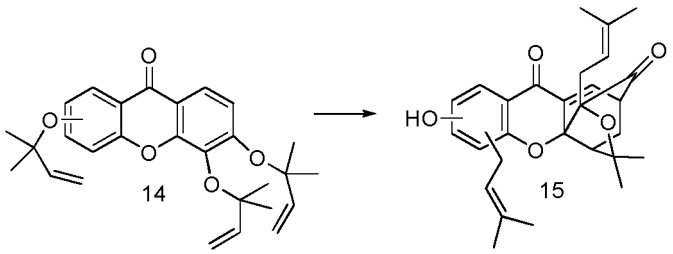
[0018] The compound 12 is obtained via oxidation of the compound 11, wherein the reaction temperature is 25°C - 40°C, and the preferred oxidants are SnO_2 and t-butyl hydroperoxide, lead tetraacetate, and the like. The solvent is selected from toluene, dichloromethane, trichloromethane ,DMF, and the like.



[0019] When R_1 is double substituted by a hydroxyl group and an isopentene group, the compound 5 reacts with chloro-methyl-butyne, and as a result, the compound 13 is obtained, wherein the reaction temperature is 60°C - 90°C, and the solvent is selected from DMF, acetone, acetonitrile, dichloromethane, trichloromethane, and the like. An inorganic alkali or organic alkali, for instance, NaOH, KOH, K_2CO_3, or triethylamine should be added to the reaction, and CuCl, CuI, or KI should also be added as catalyst.



[0020] The compound 14 is obtained via hydrogenation of the compound 13 at normal pressure, wherein the reaction temperature is 20°C - 50°C; the solvent is selected from ethyl acetate, THF, acetonitrile, ethanol, and the like; and a hydrogenation catalyst, for instance, 5% Pd/C, 10% Pd/C, 5% Pd-$BaSO_4$, 10% Pd-$BaSO_4$, and the like should also be added.



[0021] The compound 14 is heated to be rearranged, as a result, the compound 15 is obtained, wherein the reaction temperature is 120°C - 180°C, and the solvent is selected from toluene, DMF, diphenyl ether, and the like.

[0022] The compound of Formula (I) is purified by a common separation method, for instance, recrystallization, column chromatography, and the like.

[0023] The present invention also includes a hydrate, a stereomer, and/or a solvate of compound of Formula (I).

[0024] A pharmaceutically acceptable carrier, for instance, a tablet, a capsule, a powder, a syrup, a liquid, a suspension, or an injection could be a carrier for the compound of the present invention so as to form normal pharmaceutical preparations, and furthermore, the normal pharmaceutic adjuvants, for instance, a flavor, a sweetening agent, a liquid or solid filler, or a thinner, could also be included in the carrier for the compound of the present invention.

[0025] The compound of the present invention could be served as an oral or injection manner in the clinical administration.

[0026] The clinical dosage of the compound of present invention is 0.01 mg/day to 1000mg/day, furthermore, according to the health conditions and dosage types, the clinical dosage which may deviate from said range could also be accepted.

[0027] The results obtained from the pharmaceutical test show that the compound of the present invention has relatively strong anti-proliferative activity with the tumor cells, which is comparable with that of natural gambogic acid. Therefore, the compound of the present invention might be an attractive ingredient for use in the development of anti-tumor drugs.

[0028] The results obtained from the pharmaceutical test by using partial compounds of the present invention are as shown below:

Test method: The cells of log phase are cultivated in the culture plate with 96 pores, and each pore contains 100μL of solution (including 1000 - 1200 tumor cells). The next day, different concentrations of the present compound are added to the treatment groups, each compound contains 4 to 5 dosage groups, and each dosage group contains at least 3 parallel pores. The solvent with an equivalent volume of the said compound is added to the control groups. The said culture plate is then placed in a 5% CO_2 incubator, cultured at 37°C, and the culture solution is discharged 4 days later. Next, 200μL of the 0.2% MTT solution (RPMI1640 preparation) is added to each pore and incubated at 37°C for 4 hours; the obtained supernatant is discharged; and 150μL of DMSO is added to each pore so as to dissolve formazane particles. After slightly shaking the mixture, the optical density (OD) is measured by the ELIASA in the conditions of a resulting reference wavelength 450nm and a detection wavelength 570nm.

[0029] The tumor cells treated with solvent are used as control groups, and the inhibition rate of the drugs against the tumor cells and IC50 are calculated according to the following equation. The obtained results are shown in Table 1 which displays the antiproliferative activity of the tumor cells IC_{50} of the compound. The MCF-7 cells are human breast cancer cells and the BGC-823 cells are human gastric carcinoma cells.

$$\text{Inhibition rate} = \frac{\text{Average OD of comparison group - Average OD of treatment group}}{\text{Average OD of comparison group}} \times 100\%$$

Table 1: Antiproliferative activity of the tumor cells IC_{50} of the compound.

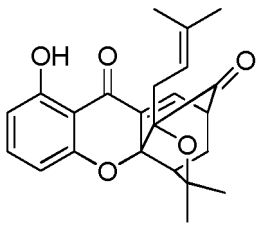
Compound No.	Corresponding Examples	MCF-7 cell IC_{50} (μM)	BGC-823 cell IC_{50} (μM)
CPUY I-1	Example 1	9.16	3.59
CPUY I-2	Example 4	12.40	17.60
CPUY I-5	Example 10	5.79	15.00
CPUY I-6	Example 11	11.90	21.70
CPUY I-7	Example 12	10.90	18.20
CPUY I-8	Example 13	9.06	11.30
II		13.90	20.30
Gambogic acid		2.19	2.35

[0030] The present invention possesses the following advantages: the natural product of gambogic acid is not necessary to be used as raw material, instead the structurally simplified analogue of the gambogic acid (Formula (1)) can be directly prepared; the obtained structure is simple in comparison with that of the gambogic acid; the anti-tumor activity is the same as that of gambogic acid; and the obtained anti-tumor activity that resulted from the hydroxyl substitution is higher than that of the reported Compound (II).

Detailed description of the preferred embodiments

Example 1

[0031] The following formula represents a 3,3a,4,5-tetrahydro-3,3-dimethyl-1-(3-methyl-2-butenyl)-8-hydroxyl-1,5-dimethylene-1H,7H-furan[3,4-d]xanthene-7,13-diketon e endocyclic compound (CPUY I-1).



(1) Preparation of 1, 5, 6-trimethoxy-9H-xanthenone:

[0032] In preparation of 1, 5, 6-trimethoxy-9H-xanthenone, 9.6g (52.8mmol) of 2,6-dimethoxy benzoic acid is dissolved in 140mL of dried benzene, 24mL of oxalyl chloride is added and mixed at room temperature for 24 hours. Subsequently, the solvent and remaining oxalyl chloride are removed via vacuum distillation; 160mL of dried ethyl ether is added to dissolve the remains; 8.8g (52.4mmol) of 1,2,3-trimethoxybenzene is added; the mixture is stirred for 30 minutes in an ice-bath; 20g (152mmol) of anhydrate $AlCl_3$ is added and reacted at room temperature for 20 hours; the over amount of $AlCl_3$ is quenched with the diluted HCl solution (15%) and then extracted with ethyl acetate (2×100mL); the organic phase is dried with anhydrous sodium sulfate and condensed; and as a result, 16g of yellow solid is obtained. The obtained solid is directly dispersed in 240mL of mixed solution containing methanol and water (methanol: water = 5:3) without purification; 23.2g (58.36mmol) of NaOH is added; the mixture is stirred and refluxed at 110°C for 36 hours; 6mol/L of HCl is added until the pH value is adjusted to 6 - 8; and as a result, a large amount of solid is precipitated. The said precipitation is filtered, and the resulting filter cake is purified with the aid of column chromatography, wherein

the eluent is the mixed solution containing petroleum ether and ethyl acetate (petroleum ether: ethyl acetate = 4: 1), and as a result, 12.8g white solid is obtained, and the productivity is 85%; m.p. is 144.6°C - 145.7°C; 1H-NMR (300MHz, CD3COCD3): 3.95(m, 6H), 4.01(s, 3H), 6.97(d, 1H, J1=8.4Hz, J2=0.6Hz), 7.14(d, 1H, J1=8.4Hz, J2=0.6Hz), 7.15(d, 1H, J=9.0Hz), 7.69(t, 1H, J=8.4Hz), 7.89(d, 1H, J=9Hz); EI-MS(m/z): 286 (M+).

(2) Preparation of 1, 5, 6-trihydroxy-9H-xanthenone:

[0033] In preparation of 1,5,6-trihydroxy-9H-xanthenone, 15g (52.5mmol) of 1,5,6-trimethoxy- 9H-xanthenone is dissolved in 500mL of mixed solution (HBr: acetic acid = 1:2), the said mixture is heated to 120°C, and refluxed for 12 hours. Next, 10% NaOH solution is added until the pH value is adjusted to 3 - 4, and as a result, a large amount of gray solid is precipitated. The said precipitation is filtered, and as a result, 9g of grey solid is obtained, and the productivity is 70%; m.p. is 300°C - 301°C; 1H-NMR (300MHz, DMSO-d6): 6.77(dd, 1H, J1=8.3Hz, J2=0.87Hz,), 6.97(d, 1H, J=8.8Hz), δ7.05(dd, 1H, J1=8.3Hz, J2=0.87Hz), 7.57(d, 1H, J=8.8Hz), 7.68(t, 1H, J=8.3Hz), 9.53(s, 1H), 10.68(s, 1H), 12.91 (s, 1H); ESI-MS(m/z): 243 ([M-H]-).

(3) Preparation of 7-hydroxy-2, 2-diphenyl-6H-[1, 3]dioxolo[4, 5-c]-6-xanthenone:

[0034] In preparation of 7-hydroxy-2, 2-dihenyl-6H-[1,3]dioxolo[4, 5-c]-6-xanthenone, 5g (22.3mmol) of 1,5,6-trihydroxy-9H-xanthenone is added to 40mL of diphenyl ether, subsequently, 7mL (35mmol) of diphenyl dichloromethane is added, and the mixture reacts at 175°C for 4 hours. After the reaction solution is cooled, 800mL petroleum ether is added, and as a result, a large amount of gray solid is precipitated. The said precipitation is filtered and purified with the aid of column chromatography, wherein the eluent is the mixed solution containing petroleum ether and ethyl acetate (petroleum ether:ethyl acetate = 8: 1), and as a result, 6.1g of light yellow solid is obtained, and the yield is 79%; m.p. is 203°C - 205 °C; 1H-NMR (300 MHz, CDCl3): 6.72(d, J = 8.4Hz, 1H), 6.90 (d, J =9.3Hz, 1H), 6.93 (d, J = 9.3Hz, 1H), 7.34 (m, 6H), 7.49 (t, J = 9.3Hz,1H), 7.57 (m, 4H), 7.82 (d, J = 8.4Hz, 1H), 12.70 (s, 1H) ; EI-MS(m/z): 408.

(4) Preparation of 7-methoxy methylenedioxy-2, 2-diphenyl-6H-[1,3]dioxolo[4,5-c] xanthenone:

[0035] In preparation of 7-methoxy methylenedioxy-2, 2-diphenyl-6H-[1,3]dioxolo[4,5-c] xanthenone, 6.1 g (14.85mmol) of 7-hydroxy-2,2-diphenyl-6H-[1,3]dioxolo[4,5-c]- 6-xanthenone is dissolved in 200mL of acetone, 1.2g (29.7mmol) of NaH is added, the mixture is mixed at 0 °C for 0.5 hours, 2.43mL (29.7mmol) chloromethyl methyl ether is added, and at the end of addition, the mixture reacts at room temperature for 8 hours. The reaction solution is then poured into 800mL of ice water, and as a result, a large amount of white solid is precipitated. The said precipitation is filtered and dried, and as a result, 6g of white solid is obtained, and the yield is 90%; m.p. is 138 °C - 140°C; 1H-NMR (300 MHz, CDCl3): 3.56 (s, 3H), 5.36 (s, 2H), 6.94(d, J = 8.4Hz, 1H), 7.04 (dd, 1H, J1=8.2Hz, J2=0.6Hz, 1H), 7.17 (dd, J= 8.2Hz, J2=0.6Hz, 1H), 7.40 (m, 6H), 7.55 (dd, J = 8.2H, J2=0.6Hz), 7.64 (m, 4H), 7.89 (d, J = 8.4Hz, 1H) ; EI-MS(m/z): 452(M+).

(5) Preparation of 3, 4-dihydroxy-7-methoxy methylenedioxy-9H-xanthenone:

[0036] In preparation of 3, 4-dihydroxy-7-methoxy methylenedioxy-9H- xanthenone, 6g (13.2mmol) of 7-methoxy methylenedioxy-2,2-diphenyl-6H-[1,3]dioxolo[4,5-c] xanthenone is dissolved in 420ml of mixed solution containing methanol: THF = 1:1, 700mg of 10% Pd/C is added, and the mixture undergoes hydrogenation at normal pressure for 24 hours. The reaction solution is filtered, the filtrate is condensed, the residue is purified with the aid of column chromatography (petroleum ether /ethyl acetate = 1:1), and as a result, 3g of dark green solid is obtained, and the yield is 78.5%; m.p. is greater than 300°C; 1H NMR(300MHz, DMSO): 3.46(s, 3H), 5.31 (s, 2H), 6.90(d, 1H, J=8.25Hz), 7.02(dd, 1H, J1=8.8Hz, J2=2.2Hz), 7.14(dd, J1=8.8Hz, J2=2.2Hz), 7.84(dd, 1H, J1=8.8Hz, J2=2.2Hz), 8.25(d, 1H, J=8.25Hz); EI-MS (m/z) 288(M+), 288, 256, 244.

(6) Preparation of 1-hydroxy-5, 6-dimethyl butynyloxy-9H-xanthenone

[0037] In preparation of 1-hydroxy-5, 6-dimethyl butynyloxy-9H-xanthenone, 3g (10.2mmol) of 3,4-dihydroxy-7-methoxy methylenedioxy-9H-xanthenone is dissolved in 200mL of acetonitrile, and subsequently, KI (1.73g, 10.2mmol), 1,8-diazabicyclo-dicyclo (5,4,0)-7-undecene (7.2mL, 57.12mmol), and CuI (300mg,1.6mmol) are added, respectively. The said mixture is stirred at room temperature for 10 minutes; is placed in an ice-bath; chloro-methyl-butyne (8.4ml, 81.6mmol) is added; and the said mixture then reacts at room temperature for 48 hours.

[0038] It is then vacuum distilled to condense acetonitrile; 800mL of water and 200mL of ethyl ether are added; and 2mol/L of HCl are added until the pH value is adjusted to 3. The mixture is stirred at room temperature for 4 hours; the

water phase is extracted with 800mL of ethyl acetate four times; the extracted ethyl acetate is dried with anhydrous sodium sulfate; the organic phase is condensed; the resulting residue is purified with the aid of column chromatography, wherein the eluent is the mixed solution containing petroleum ether and ethyl acetate(petroleum ether : ethyl acetate = 8: 1); and as a result, 2g of brown crystals are obtained, and the productivity is 49%; m.p. is 138°C - 140°C; 1 H-NMR (300 MHz, CDCl3): 1.79 (s, 6H), 1.83 (s, 6H), 2.28 (s, 1H), 2.66 (s, 1H), 6.79 (dd, J1=8.1Hz, J2=0.6Hz, 1H), 6.95 (dd, J1=8.1Hz, J2=0.6Hz, 1H), 7.56 (t, J = 8.1 Hz, 1H), 7.66 (d, J = 9Hz, 1H), 7.98 (d, J = 9Hz, 1H), 12.71 (s, 1H); EI-MS(m/z): 376, 310,244.

(7) Preparation of 1-hydroxy-5, 6-dimethyl butenyl-9H-xanthenone:

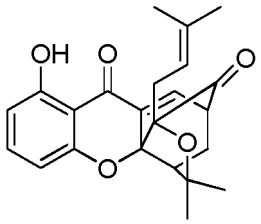
[0039] In preparation of 1-hydroxy-5, 6-dimethyl butenyl-9H-xanthenone, 1-hydroxy-5, 6-dimethyoxy butynyloxy-9H-xanthenone (2g, 5.3mmol) is dissolved in 18mL of ethanol, 50mg of 10% $Pd/BaSO_4$ is added, and the mixture undergoes hydrogenation at normal pressure for 12 hours. The obtained is filtered, the reaction solution is condensed, and the obtained gray solid is washed with petroleum ether and is used directly in the following step.

(8) Preparation of the 3, 3a, 4, 5-tetrahydro-3, 3-dimethyl-1-(3-methyl-2-butenyl) -8-hydroxy-1,5-dimethylene-1 H, 7H-furan[3, 4-d]xanthene-7, 13-diketone endocyclic compound:

[0040] In preparation of the 3, 3a, 4, 5-tetrahydro-3, 3-dimethyl-1- (3-methyl-2-butenyl) -8-hydroxy-1, 5-dimethylene-1H, 7H-furan[3, 4-d]xanthene-7, 13-diketone endocyclic compound, 1.8g of 1-hydroxy-5,6-dimethyl butenyl-9H-xanthenone is dissolved in 15mL of DMF and the said mixture reacts at 125°C for 6 hours. The solvent is evaporated, the resulting residue is purified with the aid of column chromatography (petroleum ether /ethyl acetate = 6: 1), and as a result, 1.2g brown solid is obtained, and the yield is 66%. The obtained solid is further crystallized in the mixed solution containing acetone and petroleum ether (acetone: petroleum ether = 1: 20), and the brown crystal is obtained, and the m.p. is 130°C - 132°C; 1H-NMR (300 MHz, CDCl3): 0.95 (s, 3H), 1.18-1.25 (m, 4H), 1.30 (s, 3H), 1.61 (s, 3H), 2.26 (dd, J1 = 13.5Hz, J2 = 4.5Hz, 1H), 2.37 (d, J = 9.6, 1H), 2.54 (d, J = 7.8Hz, 2H), 3.44 (dd, J1 = 6.9Hz, J2 = 4.5Hz, 1H), 4.34 (m, 1H), 6.43 (dd, J1 = 8.Hz, J2 = 0.9Hz, 1H), 6.45 (dd, J1 = 8.Hz, J2 = 0.9Hz, 1H), 7.32 (t, J = 8.1 Hz, 1H), 7.41 (d, J = 9.6 Hz, 1H), 12.00 (s, 1H).

Example 2

[0041] The following formula represents a 3,3a,4,5-tetrahydro-3,3-dimethyl-1-(3-methyl-2-butenyl)-8-hydroxyl-1,5-dimethylene-1H,7H-furan[3,4-d]xanthene-7,13-diketone endocyclic compound (CPUY I-1).



(1) Preparation of 5,6-dihydroxyl-1-acetoxy xanthenone:

[0042] In preparation of 5,6-dihydroxyl-1-acetoxy xanthenone, 5g (20.5mmol) of 1,5,6-trihydroxy-9H-xanthenone is dissolved in 35mL of DMF; subsequently, 5g of K_2CO_3, 500mg of KI, and 7mL (61mmol) of benzyl chloride are added; the said mixture reacts at 65°C for 2 hours; the reaction solution is cooled and transferred to 2mol/L of HCl; and as a result, a large amount of solid is precipitated. The said precipitation is vacuum filtered and dried, and as a result, 8g of light yellow solid 5,6-dibenzyl-1-hydroxyl-xanthenone is obtained. The said obtained solid is directly dissolved in 80mL of dichloromethane, subsequently, 5g of DMAP and 6mL of acetic anhydride are added in turn, and the said mixture reacts at a constant temperature of 25°C for 2 hours. The obtained reaction solution is washed twice with saturated NH_4Cl solution (80mL x 2) and twice with water (80mL x 2); the obtained organic phase is dried with anhydrous sodium sulfate; and 8g of white solid 5,6-dibenzyl-1- acetyl xanthenone is obtained via vacuum condensation. The said obtained solid is dissolved in 400mL of mixed solution containing THF and methanol (THF:methanol = 1: 1), and hydrogenation takes place under normal pressure with the aid of 10% Pd/C. The said mixture reacts at a constant temperature of 40°C for 2 hours; the obtained substance is filtered; the filtrate is condensed; 200mL of petroleum ether is added to wash the resulting residue; 4.5g of grey solid is obtained via vacuum filtration; and the obtained solid is directly used in the following

step without purification.

(2) Preparation of 5,6-dimethyl butynyl-1-acetoxy xanthenone:

[0043] In preparation of 5,6-dimethyl butynyl-1-acetoxy xanthenone, 5,6-dihydroxy-1-acetoxy xanthenone (5g, 17.5mmol) is dissolved in 80mL of acetone, and 5g of K_2CO_3, 5g of KI, 1g of CuI, and 7mL of chloro-methyl-butyne are added in turn. The said mixture is heated and refluxed for 5 hours. At the end of the reaction, 300mL of water and 80mL of ethyl acetate are added and mixed; and the organic phase is separated and dried with anhydrous sodium sulfate. The obtained is separated with the aid of column chromatography (petroleum ether: ethyl acetate = 8: 1) and 3g of yellow solid is obtained, and the yield is 41%; 1H-NMR (300 MHz, $CDCl_3$): 1.76 (s, 3H), 1.82(s, 3H), 2.31 (s, 1H), 2.50 (s, 3H), 2.65 (s, 1H), 6.97 (d, J=7.5Hz, 1H), 7.42 (d, J=8.4Hz, 1H), 7.59-7.69 (m, 2H), 7.95 (s, J=9Hz, 1 H).

(3) Preparation of 5,6-dimethyl butenyl-1-acetoxy xanthenone:

[0044] In preparation of 5,6-dimethyl butenyl-1-acetoxy xanthenone, 5,6-bis(dimethyl butynyl-1-acetoxy xanthenone (3g, 12.3mmol) is dissolved in 70mL of mixed solution containing ethyl acetate and ethanol (ethyl acetate : ethanol =1: 3), and undergoes hydrogenation at normal pressure with the aid of 300mg 10% Pd-$BaSO_4$. The obtained reacts at room temperature for 16 hours; the reaction solution is filtered; and the solvent is condensed and dried in reduced pressure, and is used directly in the following step.

(4) 3,3a,4,5-tetrahydro-3,3-dimethyl-1-(3-methyl-2-butenyl)-8-acetoxy-1,5-di methylene -1 H,7H-furan[3, 4-d]xanthene-7,13-diketone endocyclic compound:

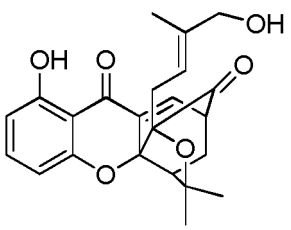
[0045] In preparation of the above compound, 1-hydroxyl-5,6-dimethyl butenyl-9H-xanthenone (1.8g, 7.3mmol) is dissolved in 15mL of DMF and the said mixture reacts at 125°C for 6 hours and the solvent is evaporated. The resulting residue is separated with the aid of column chromatography (petroleum ether: ethyl acetate = 6: 1), and as a result, 1 g of yellow solid is obtained, and the yield is 55.6%; 1 H-NMR (300 MHz, CDCl3): 0.99 (s, 3H), 1.18-1.25 (m, 4H), 1.30 (s, 3H), 1.61 (s, 3H), 2.26 (dd, J1 = 13.5Hz, J2 = 4.5Hz, 1 H), 2.28(s, 3H), 2.37 (d, J = 9.6, 1H), 2.54 (d, J = 7.8Hz, 2H), 3.44 (dd, J1 = 6.9Hz, J2 = 4.5Hz, 1 H), 4.34 (m, 1H), 6.43 (dd, J1 = 8.Hz, J2 = 0.9Hz, 1H), 6.45 (dd, J1 = 8.Hz, J2 = 0.9Hz, 1H), 7.32 (t, J = 8.1 Hz, 1H), 7.41 (d, J = 9.6 Hz, 1H).

(5) 3,3a,4,5-tetrahydro-3,3-dimethyl-1-(3-methyl-2-butenyl)-8-hydroxyl-1,5-dimethylene1H, 7H-furan[3, 4-d]xanthene-7,13-diketone endocyclic compound:

[0046] In preparation of the above compound, 3,3a,4,5-tetrahydro-3,3-dimethyl-1 -(3-methyl-2-butenyl)-8-acetoxy-1,5-dimethylene-1H,7H-furan[3,4-d]xanthene-7,13-diketone endocyclic compound (1 g, 4mmol) is dissolved in 10mL of mixed solution containing THF and methanol (THF : methanol =1: 1), subsequently, 4mL (4mol/L) of HCl is added and the mixture is mixed at room temperature for 6 hours, 10mL ethyl acetate and 10mL 10% $NaHCO_3$ are added, and the obtained organic phase is separated and dried with anhydrous sodium sulfate. The obtained is separated with the aid of column chromatography (petroleum ether: ethyl acetate = 4: 1), and as a result, 810mg of yellow solid is obtained, and the productivity is 90%; m.p. is 130°C - 132°C; 1H-NMR (300 MHz, CDCl3): 0.95 (s, 3H), 1.18-1.25 (m, 4H), 1.30 (s, 3H), 1.61 (s, 3H), 2.26 (dd, J1 = 13.5Hz, J2 = 4.5Hz, 1H), 2.37 (d, J = 9.6, 1H), 2.54 (d, J = 7.8Hz, 2H), 3.42 (dd, J1 = 6.9Hz, J2 = 4.5Hz, 1H), 4.33 (m, 1H), 6.43 (dd, J1 = 8.Hz, J2 = 0.9Hz, 1H), 6.45 (dd, J1 = 8.1 Hz, J2 = 0.9Hz, 1H), 7.32 (t, J = 8.1 Hz, 1H), 7.41 (d, J = 9.6 Hz, 1H), 12.00 (s, 1 H).

Example 3

[0047] The following formula represents a (E)-3,3a,4,5-tetrahydro-3,3-dimethyl-1-(3-hydroxymethyl-2-butenyl)-8-hydroxy-1,5-dimethylene-1H,7H-furan[3,4-d]xan thene-7, 13-diketone endocyclic compound:



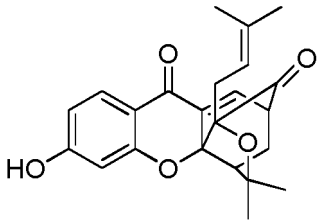
(1) The synthetic method in preparation of 3,3a,4,5-tetrahydro-3,3-dimethyl-1-(3-methyl-2-butenyl)-8-hydroxy-1,5-dimethylen e-1H, 7H-furan[3, 4-d]xanthene-7, 13-diketone endocyclic compound is same as those described in Example 1 and Example 2.

(2) In preparation of (E)-3,3a,4,5-tetrahydro-3,3-dimethyl-1-(3-hydroxymethyl-2- butenyl)-8-hydroxyl-1,5-dimethylene-1 H, 7H-furan[3, 4-d]xanthene-7, 13- diketone endocyclic compound:

[0048] 800 mg of 3,3a,4,5-tetrahydro-3,3-dimethyl-1-(3-methyl-2-butenyl)-8-hydroxy-1,5-dimethylene-1H,7H-furan[3,4-d]xanthene-7,13-diketone endocyclic compound is dissolved in 5mL of dichloromethane, 80mg of SnO_2 and 1ml of t-butyl hydroperoxide are added, and the said mixture is stirred at room temperature for 24 hours. After the reaction, the obtained is washed with water three times, the organic phase is separated, and is then separated again with the aid of column chromatography (petroleum ether: ethyl acetate = 2: 1), and as a result, 780mg of yellow solid is obtained, and the yield is 94%.

Example 4

[0049] The following formula represents a 3,3a,4,5-tetrahydro-3,3-dimethyl-1-(3-methyl-2-butenyl)-10-hydroxyl-1,5-dimethylene-1H,7H-furan[3,4-d] xanthene-7, 13-diketone endocyclic compound (CPUY I-2).



(1) Preparation of 3-hydroxyl-4, 6-dimethoxy-9H-xanthenone:

[0050] In preparation of 3-hydroxyl-4, 6-dimethoxy-9H-xanthenone, 2.4g (13.14mmol) of 2,4-dimethoxy benzoic acid is dissolved in 60mL of dried dichloromethane, 5mL of oxalyl chloride is added, and the said mixture is stirred at room temperature for 24 hours. Once the solvent is evaporated, 80mL of ethyl ether is added to dissolve resulting residue; 2.19g (13.03mmol) of 1,2,3-trimethoxy benzene is added; the said mixture is cooled in an ice-bath for 30min; 5.0g of anhydrate $AlCl_3$(37.5mmol) is added; the said mixture reacts at room temperature for 12 hours; and the over amount of $AlCl_3$ is quenched with the aid of diluted HCl solution (15%). The obtained is then extracted with ethyl acetate (80mL x 2) and dried with anhydrous sodium sulfate. The resulting residue is condensed in reduced pressure and is directly dissolved in the mixed solution containing methanol (20mL) and 30% NaOH (40mL). The said mixture is heated and refluxed for 14 hours, the pH value of the obtained solution is adjusted with the aid of 6mol/L HCl until the pH value reaches 6, the said mixture is vacuum filtered and dried, and as a result, 3g of crude product is obtained, and the yield is 81%; m.p. is 120.2°C - 121.2°C ; 1H-NMR (300MHz, CD3COCD3): 3.98-4.03(m, 9H), 7.00 (dd, 1H, J1= 8.9Hz, J2=2.4Hz), 7.09(d, 1H, J=2.4Hz), 7.19(d, 1H, J=9.0Hz), 7.95(d, 1H, J=9.0Hz), 8.13(d, 1H, J=8.9Hz) ; EI-MS(m/z): 286[M+], 271, 256, 241.

(2) Preparation of 3, 4, 6-trihydroxyl-9H-xanthenone:

[0051] In preparation of 3, 4, 6-trihydroxyl-9H-xanthenone, 8g (2.79mmol) of 3-hydroxyl-4, 6-dimethoxy-9H-xanthenone is dissolved in 160mL of mixed solution containing HBr and acetic acid (HBr:acetic acid = 1: 2) (V: V), the said mixture is heated to 120°C and refluxed for 12 hours, the pH value of the obtained mixture is adjusted with the aid of 10% NaOH solution until the pH value reaches 3 - 4, and as a result, a large amount of grey solid is precipitated. It is then vacuum filtered and purified with the aid of silica gel column chromatography (petroleum ether/ethyl acetate = 1: 1), and as a result, 5.8g of grey solid is obtained, and the yield is 85%; m.p. is greater than 300°C (reported m.p. is 340°C - 341°C); 1H-NMR (300MHz, DMSO-d6): 6.83-6.93(m, 3H,), 7.50(d, 1H, J=8.8Hz), 8.00(d, 1H, J=8.8Hz), 9.28(s, 1H), 10.31 (s, 1H), 10.77(s, 1 H), ESI-MS(m/z): 243([M-H]-).

(3) Preparation of 9-hydroxyl-2, 2-diphenyl-6H-[1, 3]dioxolo[4, 5-c]xanthenone:

[0052] In preparation of 9-hydroxyl-2, 2-diphenyl-6H-[1, 3]dioxolo[4, 5-c]xanthenone, 5g (21mmol) of 3, 4, 6-trihydroxyl-

9H-xanthenone is added to 30mL of diphenyl ether, 7mL (36mmol) of diphenyl dichloromethane is added, and then the said mixture reacts at 175°C for 2 hours. The obtained is cooled, 100mL of petroleum ether is added, and as a result, a large amount of yellow solid is precipitated. The obtained solid is vacuum filtered and purified with the aid of filter cake column chromatography, the eluent (petroleum ether/ethyl acetate = 4: 1) is used, and as a result, 5.1 g of yellow solid is obtained, and the yield is 61%; m.p. is 231°C - 232°C; 1 H-NMR(300MHz, CD3COCD3): 6.94-6.98(m, 2H), 7.1 (d, 2H, J=8.7Hz), 7.47~7.50 (m, 6H), 7.66-7.69(m, 4H), 7.85(d, J=8.7Hz, 1H), 8.10(q, J=9Hz, 1H); EI-MS (m/z) 408[M+], 331, 303, 165.

(4) Synthesis of 9-methoxy methyleneoxy-2, 2-diphenyl-6H-[1, 3]dioxolo[4, 5-c] xanthenone:

[0053] In preparation of 9-methoxy methyleneoxy-2, 2-diphenyl-6H-[1, 3]dioxolo[4, 5-c] xanthenone, 5g (2.45mmol) of 9-hydroxyl-2, 2-diphenyl-6H-[1, 3]dioxolo[4, 5-c]xanthenone is dissolved in 70mL of DM, 515mg (4.29mmol) of sodium hydride is added, and the said mixture is mixed for 10min. Subsequently, 1.8mL (23mmol) of chloromethyl methyl etheris added; the said mixture reacts at room temperature for 8 hours; 200mL water is added to the said reaction solution; the said solution is extracted with 200mL of ethyl acetate four times; and the organic phase is condensed. The resulting residue is separated and purified with the aid of column chromatography (petroleum ether/ethyl acetate = 4: 1), and as a result, 5g of white solid is obtained, and the yield is 99%; m.p. is 179°C - 181°C ; 1H NMR(300MHz, CDCl3): 3.44(s, 3H), 5.21(s, 2H), 6.91-6.96(m, 2H), 7.10(s, J1=2.4Hz, 1H), 7.32-7.36(m, 6H), 7.54-7.59(m, 4H), 7.82(d, 1H, J=5.1Hz), 8.17(d, 1H, J=5.3Hz) ; EI-MS (m/z) 452(M+), 375, 331, 165, 105.

(5) Preparation of 3, 4-dihydroxyl-6-methoxy methyleneoxy-9H-xanthenone:

[0054] In preparation of 3, 4-dihydroxyl-6-methoxy methyleneoxy-9H-xanthenone, 5g (2.2mmol) of 9-methoxy methyleneoxy-2, 2-diphenyl-6H-[1, 3]dioxolo[4, 5-c] xanthenone is added to 90ml of mixed solution containing ethanol and THF (ethanol: THF = 1: 1), 500mg of 10% Pd/C is added, and the said mixture undergoes hydrogenation at normal pressure for 24 hours. The obtained reaction solution is vacuum filtered and the filtrate is condensed. The resulting residue is separated and purified with the aid of column chromatography (petroleum ether: ethyl acetate = 2: 1), and as a result, 5g of light yellow solid is obtained, and the yield is 90%; m.p. is greater than 300°C; 1H NMR (300MHz, DMSO-d6): 3.52(s, 3H), 5.30(s, 2H), 6.97(d, J=8.8Hz, 1H), 7.04-7.07(q, J1=2.2Hz, J2=8.8Hz, 1H), 7.14(d, J=2.2Hz, 1H), 7.84(d, J=8.8Hz, 1H), 8.25(d, J=8.8Hz, 1H) ; EI-MS (m/z) 288(M+), 258, 215, 187, 167.

(6) Preparation of 3, 4-dimethyl butynyl-6-methoxy methyleneoxy-9H-xanthenone:

[0055] In preparation of 3, 4-dimethyl butynyl-6-methoxy methyleneoxy-9H-xanthenone, 5g (16.5mmol) of xanthenone is dissolved in 80mL of acetonitrile, and subsequently, 2.5g (20mmol) of KI, 9.5mL of DBU, and 250mg (0.028mmol) of CuI are added in turn. Then 0.42ml (3.3mmol) of chloro-methyl butyne is added; the said mixture reacts at room temperature for 24 hours; 800mL water is added; the said mixture is stirred at room temperature for 15min; the obtained water phase is extracted with 200mL ethyl acetate four times; and the obtained organic phase is condensed. The resulting residue is separated and purified with the aid of column chromatography, the eluent (petroleum ether/ethyl acetate = 8: 1) is used, and as a result, 3.5g of orange powder is obtained, and the yield is 45%; m.p. is 128°C - 130°C; 1H-NMR (300 MHz, $CDCl_3$): 1.69 (s, 6H), 1.75 (s, 6H), 2.26 (s, 1H), 2.58 (s, 1H), 3.45 (s, 3H), 5.22 (s, 1H), 6.96 (d, J1=8.7Hz, J2=2.1Hz, 1H), 7.04 (d, J=2.1 Hz, 1H), 7.54 (d, J = 9Hz, 1H), 7.97 (s, J=9Hz,1H), 8.18 (d, J = 8.7Hz, 1H) ; EI-MS(m/z): 420, 405, 377, 354, 339, 324, 309, 295, 288, 244.

(7) Preparation of 2-methoxy methyleneoxy-5, 6-dimethyl butenyl-9H-xanthenone:

[0056] In preparation of 2-methoxy methyleneoxy-5, 6-dimethyl butenyl-9H-xanthenone, 3.5g of xanthenone is dissolved in 80mL of ethanol, 350mg of 10% Pd-$BaSO_4$ is added, and the said mixture undergoes hydrogenation at room temperature for 2 hours. The obtained reaction solution is vacuum filtered and the obtained filtrate is condensed. The resulting residue is separated and purified with the aid of column chromatography, the eluent (petroleum ether/ethyl acetate = 8: 1) is used, and as a result, 3g of colorless oil is obtained, the yield is 89%, and the said obtained is used directly in the following reaction step.

(8) Preparation of 3, 3a, 4, 5-tetrahydro-3,3-dimethyl-1-(3-methyl-2-butenyl) -10-methoxy methyleneoxy-1, 5-dimethylene-1 H, 7H-furan[3, 4-d]xanthene-7, 13-diketone:

[0057] In preparation of 3, 3a, 4, 5-tetrahydro-3,3-dimethyl-1-(3-methyl-2-butenyl) -10-methoxy methyleneoxy-1, 5-dimethylene-1H, 7H-furan[3, 4-d]xanthene-7, 13-diketone, 3g of 2-methoxy methyleneoxy-5, 6-methyl butenyl-9H-xan-

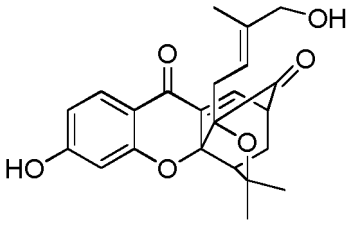
thenone is dissolved in 30mL of DMF, the said mixture reacts at 125°C for 6 hours, and the solvent is evaporated. The obtained residue is separated and purified with the aid of column chromatography, and as a result, 1.4g of white solid is obtained, and the yield is 45%; m.p. is 168°C - 169°C; 1H-NMR (300 MHz, CDCl3): 0.92 (s, 3H), 1.17-1.29 (m, 7H), 1.63 (s, 3H), 2.24 (dd, J1 = 13.5Hz, J2 = 4.5Hz, 1H), 2.37 (d, J = 9.6, 1H), 2.51 (d, J = 9.3Hz, 2H), 3.36-3.44 (m, 4H), 4.36 (m, 1H), 5.15 (s, 2H), 6.57 (d, J = 2.1 Hz, 1H), 6.64 (dd, J1 = 8.7Hz, J2 = 2.1 Hz, 1H), 7.31 (d, J = 6.9 Hz, 1H), 7.80 (d, J = 8.7 Hz, 1H) ; IR (KBr): 2974.4, 2909.6, 1737.2, 1647.4, 1611.2, 1499.2, 1438.5, 1290.5, 1150.5, 1079.2, 1009.2, 982.4 ; EI-MS(m/z): 424, 396, 381, 368, 353, 327, 299, 285, 257 ; Anal. Calcd for C25H28O6 (%): C 70.74, H 6.65; Found: C70.64, H 6.95.

(9) Preparation of 3, 3a, 4, 5-tetrahydro-3,3-dimethyl-1-(3-methyl-2-butenyl) -10-hydroxy-1, 5-dimethylene-1 H, 7H-furan[3, 4-d]xanthene-7, 13-diketone:

[0058] In preparation of 3, 3a, 4, 5-tetrahydro-3,3-dimethyl-1-(3-methyl-2-butenyl) -10-hydroxy-1, 5-dimethylene-1H, 7H-furan[3, 4-d]xanthene-7, 13-diketone, 1.4g of 3, 3a, 4, 5-tetrahydro-3,3-dimethyl-1-(3-methyl-2-butenyl)-10-methoxy methyleneoxy-1, 5-dimethylene-1H, 7H-furan[3, 4-d]xanthenoid-7, 13-diketone is dissolved in 18mL of mixed solution containing dichloromethane and ethyl ether (dichloromethane: ethyl ether = 1: 1), the said mixture is cooled in an ice-bath, 10mL of concentrated HCl is added, and the said mixture reacts at room temperature for 1 hour. After the reaction, the said reaction solution is extracted with ethyl acetate, and washed with saturated NaCl solution. The ethyl ester phase is dried and condensed, and then separated and purified with the aid of column chromatography, the eluent (petroleum ether/ethyl acetate = 4: 1) is used, and as a result, 686mg of yellow solid is obtained, and the yield is 50%; m.p. is 197°C - 199°C; 1H-NMR (300 MHz, DMSO): 1.02 (s, 3H), 1.22-1.33(m, 7H), 1.68 (s, 3H), 2.31 (dd, J1 = 13.5Hz, , J2 = 3.9Hz, 1H), 2.42-2.57 (m, 3H), 3.49 (d, J = 6.6Hz, 1H), 4.4 (m, 1H), 6.46 (s, 1H), 6.63 (d, J = 9 Hz, 1H), 7.37 (d, J = 6.9Hz, 1H), 7.46 (d, J =9, 1H) ; IR (KBr): 3376, 3275.5, 2970.6, 2927.1, 1738, 1650, 1607, 1584, 1493, 1332, 1278, 1233.5, 1146, 958, 866, 745; EI-MS(m/z): 379([M-H]+) ; Anal. Calcd for $C_{23}H_{24}O_5$ (%): C 72.61% H 6.36%; Found: C 72.29% H 6.54%.

Example 5

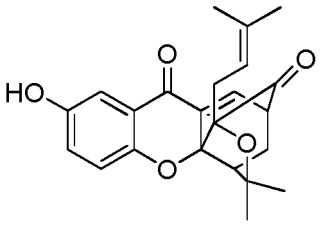
[0059] The following formula represents a 3,3a,4,5-tetrahydro-3,3-dimethyl-1-(3-hydroxymethyl-2-butenyl)-10-hydroxyl-1,5-dimethylene-1H,7H-furan[3,4-d] xanthene-7,13-diketone endocyclic compound:



[0060] The 3,3a,4,5-tetrahydro-3,3-dimethyl-1-(3-methyl-2-butenyl)-10-hydroxyl-1,5-dimethylene-1H,7H-furan[3,4-d]xanthene-7,13-diketone compound is used as a starting material, the operating procedures are the same as those described in Example 3, and as a result, 746mg of yellow solid is obtained, and the total yield is 4%.

Example 6

[0061] The following formula represents a 3,3a,4,5-tetrahydro-3,3-dimethyl-1-(3-methyl-2-butenyl)-9-hydroxyl-1,5-dimethylene-1H,7H-furan[3,4-d]xanthene -7,13-diketone endocyclic compound (CPUY I-3).

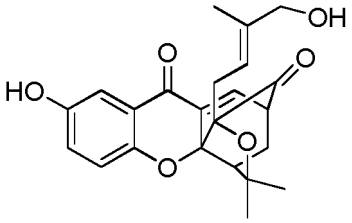


[0062] Similar to Example 4, except that the compound 2,5-dimethyoxy benzoicacid is used instead of 2,4-dimethoxy

benzoicacid, and as a result, 690mg of yellow solid is obtained, and the yield is 3.3%; m.p. is 158°C - 159°C; 1H-NMR (300 MHz, $CDCl_3$): 0.91 (s, 3H), 1.18-1.31 (m, 7H), 1.65 (s, 3H), 2.27 (dd, J1 = 13.5Hz, , J2 = 4.5Hz, 1H), 2.46 (d, J = 9.6, 1H), 2.62 (d, J = 9.3, 2H), 3.52 (t, J = 4.5Hz, 1H), 4.34 (m, 1H), 6.04 (s, 1H), 6.91 (d, J = 9 Hz, 1H), 7.06 (dd, J1 = 9Hz, , J2 = 3Hz, 1H), 7.35 (d, J =6.9Hz, 1H), 7.41 (d, J =3Hz, 1H), EI-MS(m/z): 380[M+], 352, 337, 283, 255, 213; Anal. Calcd for $C_{23}H_{24}O_5$ (%): C 72.61% H 6.36%; Found: C 72.33% H 6.50%.

Example 7

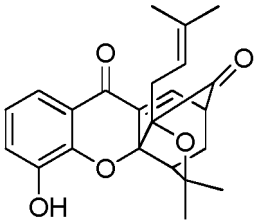
[0063] The following formula represents a 3,3a,4,5-tetrahydro-3,3-dimethyl-1-(3-hydroxymethoxy-2-butenyl)-9-hydroxyl-1,5-dimethylene-1H,7H-furan[3,4-d]xanthen e-7,13-diketone endocyclic compound.



[0064] The 3,3a,4,5-tetrahydro-3,3-dimethyl-1-(3-methyl-2-butenyl)-9-hydroxyl-1,5-dimethylene-1H,7H-furan[3, 4-d]xanthene-7,13-diketone endocyclic compound is used as starting material, the rest of the procedures are the same as those described in Example 3, and as a result, 753mg of yellow solid is obtained, and the total yield is 4%.

Example 8

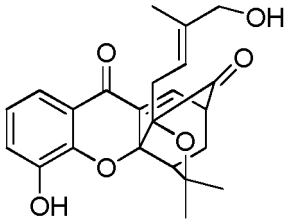
[0065] The following formula represents a 3,3a,4,5-tetrahydro-3,3-dimethyl-1-(3-methyl-2-butenyl)-11-hydroxyl-1,5-dimethylene-1H,7H-furan[3,4-d]xanthen e-7,13-diketone endocyclic compound (CPUY I-4).



[0066] Similar to Example 4, except that the compound 2,3-dimethoxy benzoic acid is used as a starting material instead of 2,4-dimethoxy benzoic acid, and as a result, 820mg of yellow solid is obtained, and the yield is 5%; m.p. is 203°C - 205 °C; 1H NMR (300 MHz, DMSO): 0.82 (s, 3H), 1.19-1.34(m, 7H), 1.64 (s, 3H), 2.27 (dd, J1 = 13.5Hz, , J2 = 4.5Hz, 1H), 2.46-2.56 (m, 3H), 3.45 (m, 1H), 4.45 (m, 1H), 5.38 (s, 1H), 6.90 (t, J= 8.1 Hz, 1H), 7.11 (dd, J1= 7.8 Hz, J1= 1.2 Hz, 1H), 7.43 (d, 1H), 7.46 (d, J =9 Hz, 1H) ; IR (KBr): 3425, 2966.2, 2925.1, 1738.22, 1650, 1607, 1583, 1493, 1377, 1279, 1233.9, 1152, 748.9; EI-MS(m/z): 380, 352, 337, 309, 283, 255, 241, 213; Anal. Calcd for C23H24O5 (%): C 72.61 % H 6.36%; Found: C 72.60%, H 6.70%.

Example 9

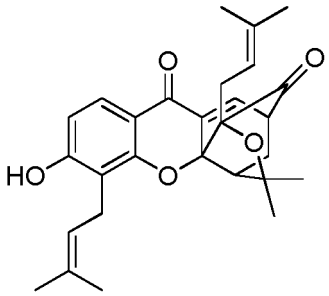
[0067] The following formula represents a 3,3a,4,5-tetrahydro-3, 3-dimethyl-1-(3-hydroxymethoxy-2-butenyl)-11-hydroxyl-1,5-dimethylene-1H,7H-furan[3,4-d]xanthene-7,13-diketone endocyclic compound.



[0068] The 3,3a,4,5-tetrahydro-3,3-dimethyl-1-(3-methyl-2-butenyl)-11-hydroxyl-1,5-dimethylene-1H,7H-furan[3,4-d]xanthene-7,13-diketone endocyclic compound is used as a starting material, the rest of procedures are same as those described in Example 3, and as a result, 755mg of yellow solid is obtained, and the yield is 4%.

Example 10

[0069] The following formula represents a 3,3a,4,5-tetrahydro-3,3-dimethyl-1,11-bis (3-methyl-2-butenyl)-10-hydroxyl-1,5-dimethylene-1H,7H-furan[3,4-d]xanthene-7,13- diketone endocyclic compound (CPUY I-5).



(Step 1) Preparation of 3, 4, 6-trimethyl butynyl-9H-xanthenone:

[0070] In preparation of 3,4,6-trimethyl butynyl-9H-xanthenone, 2.7g (11.07mmol) of 3,4,6-trimethyl-9H-xanthenone is dissolved in 100mL of acetone; subsequently, 7.34g (44.18mmol, 4equiv) of KI, 6.1 g (44.28mmol, 4equiv) of K_2CO_3 and 0.21 g (0.8mmol, 0.1 equiv) of CuI are added in turn; the said mixture is stirred at room temperature for 15min; 7.29ml (66.42mmol, 6equiv) chloro-methyl butyne is added; and the said mixture reacts at 50°C for 6 hours. The reaction solution is vacuum filtered and the filtrate is condensed. The resulting residue is separated and purified with the aid of column chromatography, the eluent (petroleum ether/ethyl acetate = 8: 1) is used, and as a result, 2.4g of orange solid is obtained, and the yield is 49%; m.p. is 117°C - 119°C, 1H NMR(300MHz, $CDCl_3$): δ 1.76 (s, 12H), 1.82 (s, 6H), 2.33 (s, 1H), 2.65 (s, 1H), 2.69 (s, 1H), 7.16 (dd, J1 = 8.7Hz, J1 = 2.1 Hz, 1H), 7.40 (d, J=2.1 Hz, 1H), 7.62 (d, J = 9.0Hz, 1H), 8.04 (d, J = 9.0Hz, 1H), 8.22 (d, J = 8.7Hz, 1H), EI-MS (m/z): 442, 427, 376, 361,324,310,281,244.

(Step 2) Preparation of 3, 4, 6-trimethyl butenyl-9H-xanthenone:

[0071] In preparation of 3,4,6-trimethyl butenyl-9H-xanthenone, 200mg of 2,5,6-trimethyl butynyl-9H-xanthenone (22) and (0.45mmol) of xanthenone are dissolved in 30mL of ethanol, 20mg of 10% Pd/$BaSO_4$ is added, and the said mixture reacts at room temperature for 4 hours. The obtained reaction solution is vacuum filtered and the filtrate is condensed. The resulting residue is separated and purified with the aid of column chromatography, the eluent (petroleum ether/ethyl acetate = 8: 1) is used, and as a result, 170mg of light green oil is obtained, and the yield is 85%; 1 H NMR(300MHz, $CDCl_3$): 1.56 (s, 12H), 1.60 (s, 6H), 5.16~5.28 (m, 6H), 6.11~6.34 (m, 3H), 6.95 (dd, J1= 9Hz, J2= 2.1 Hz ,1H), 7.05~7.10 (m, 2H), 7.89 (d, J = 9Hz, 1H), 8.14 (d, J = 9.0Hz, 1H), EI-MS (m/z): 448, 436, 420, 405, 380, 365, 325, 312, 256, 244.

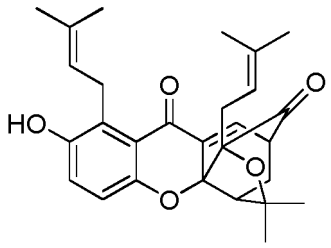
(3) Preparation of 3, 3a, 4, 5-tetrahydro-3,3-dimethyl-1, 11-bis(3-methyl-2-butenyl) -10-hydroxyl-1, 5-dimethylene-1H, 7H-furan[3, 4-d]xanthene-7, 13-diketone:

[0072] In preparation of 3,3a,4,5-tetrahydro-3,3-dimethyl-1,11-bis(3-methyl-2-butenyl) -10-hydroxyl-1, 5-dimethylene-1H, 7H-furan[3,4-d]xanthene-7,13-diketone, 120mg of 2,5,6-trimethyl butenyl-9H-xanthenone (23) is dissolved in 120ml of DMF, the said mixture reacts at 125°C for 4 hours, and subsequently, the DMF is heated and vacuum evaporated. the resulting residue is separated and purified with the aid of column chromatography, the eluent (petroleum ether/ethyl

acetate = 4: 1) is used, and as a result, 65mg of yellow solid is obtained, and the yield is 53%. The obtained is crystallized with 95% ethanol, and as a result, the orange fine crystal is obtained, and the m.p. is 158°C - 160°C; 1H NMR (300 MHz, $CDCl_3$): 0.93 (s, 3H), 1.29-1.33 (m, 7H), 1.71 (s, 3H), 1.77 (s, 3H), 1.83 (s, 3H), 2.33 (dd, J1 = 13.5Hz, J2 = 4.5Hz, 1H), 2.50 (d, J = 9.3, 1H), 2.57 (d, J = 8.7Hz, 2H), 3.46-3.55 (m, 3H), 4.40-4.45 (m, 1H), 5.28 (t, J = 6.6Hz, 1H), 6.30 (s, 1H), 6.58 (d, J=8.7Hz, 1H), 7.43 (d, J = 6.9Hz, 1H), 7.80 (d, J = 8.7 Hz, 1H), IR (KBr): 3438.7, 2964.3, 2922.1, 2849.9, 1738.9, 1649.6, 1605.3, 1433.0, 12984.6, 1262.8, 1079.6, 1046.7, 802, EI-MS(m/z): 448, 420, 405,377,351, Anal. calcd for $C_{28}H_{32}O_5.H_2O$ (%): C 72.08, H 7.35; Found: C72.33, H 7.36.

Example 11

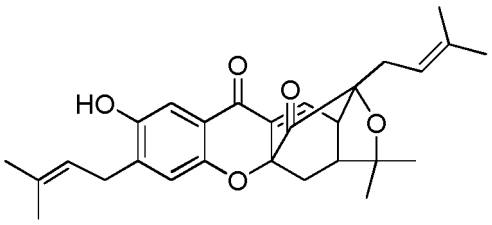
[0073] The following formula represents a 3,3a,4,5-tetrahydro-3,3-dimethyl-1,8-bis (3-methyl-2-butenyl)-9-hydroxyl-1,5-dimethylene-1H,7H-furan[3,4-d]xanthene-7 ,13- diketone endocyclic compound (CPUY I-6).



[0074] Similar to the procedures described in Example 10, except that the compound 2,5,6-hydroxyl-9H-xanthenone is used as a starting material instead of 3,4,6-trimethyl-9H-xanthenone, and as a result, 80mg of orange solid is obtained, and the yield is 40%; m.p. is 138°C - 139°C; 1H NMR (300 MHz, $CDCl_3$): δ 1.03 (s, 3H), 1.16-1.23 (m, 4H), 1.32 (s, 3H), 1.63 (s, 3H), 1.67 (s, 3H), 1.77 (s, 3H), 2.22 (dd, J1 = 13.5Hz, J2 = 4.5Hz, 1H), 2.29 (d, J = 9.6, 1H), 2.56 (d, J = 8.7Hz, 2H), 3.38 (dd, J1 = 6.9Hz, J2 = 4.5Hz, 1H), 3.88 (d, J = 6.6, 2H), 4.38 (t, J = 8.7Hz, 1H), 5.13 (t, J = 6.6, 1H), 5.39 (s, 1H), 6.81 (d, J= 9Hz, 1H), 7.00 (d, J = 9Hz, 1H), 7.18 (d, J = 6.9 Hz, 1 H), IR (KBr): 3506.1, 3171.6, 2967.4, 2918.6, 1737.0, 1659.6, 1606.3, 1486.0, 1443.5, 1376.5, 1298.6, 1221.8, 1145.25, 1042.6, 822.7, 790.5, EI-MS(m/z): 448, 420, 378, Anal. calcd for $C_{28}H_{32}O_5.H_2O$ (%): C 72.08, H 7.35; Found: C72.10, H 7.30

Example 12

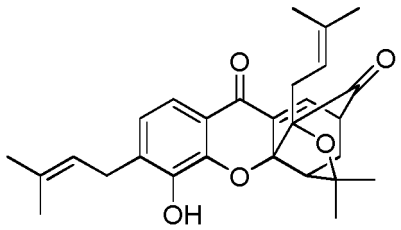
[0075] The following formula represents a 1,3a,4,11a-tetrahydro-3,3-dimethyl-1,7-bis(3-methyl-2-butenyl)-8-hydroxyl-3H-1,4a-dimethylene-10H-fura n [3,4-b] xanthene-10,12-diketone endocyclic compound (CPUY I-7).



[0076] Similar to the procedure described in Example 10, except that the compound 2,5,6-hydroxyl-9H-xanthenone is used as a starting material instead of 3,4,6-trimethyl-9H-xanthenone, and as a result, 40mg of orange crystals are obtained, and the yield is 20%; m.p. is 148°C - 150°C; 1H NMR (300 MHz, $CDCl_3$): 1.30 (s, 3H), 1.33 (s, 3H), 1.52 (s, 3H), 1.64 (s, 3H), 1.67 (s, 3H), 1.76 (s, 4H), 2.01 (dd, J1 = 8.4Hz, J2 = 14.7Hz, 1H), 2.10 (dd, J1 = 4.5, J1 = 9.9, 1H), 2.56 (d, J = 8.7Hz, 2H), 3.65 (dd, J1 = 6.9Hz, J2 = 4.5Hz, 1H), 3.82 (d, J = 6.6, 2H), 4.95 (t, J1 = 6.9Hz, J2 = 8.1Hz, 1H), 5.11 (m, 2H), 6.96 (s, 2H), 7.00 (d, J = 6.9Hz, 1H), IR (KBr): 3506.1, 3171.6, 2967.4, 2918.6, 1737.0, 1659.6, 1606.3, 1486.0, 1443.5, 1376.5, 1298.6, 1221.8, 1145.25, 1042.6, 822.7, 790.5, ESI-MS(m/z): 447([M+H]+), Anal. calcd for $C_{28}H_{32}O_5.H_2O$ (%): C 72.08, H 7.35; Found: C72.11, H 7.40.

Example 13

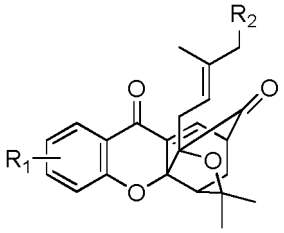
[0077] The following formula represents a 3,3a,4,5-tetrahydro-3,3-dimethyl-1,10-bis (3-methyl-2-butenyl)-11-hydroxyl-1,5-dimethylene-1H,7H-furan[3,4-d]xanthene-7, 13-diketone endocyclic compound (CPUY I-8).



[0078] Similar to the procedure described in Example 10, except that the compound 3,4,5-trihydroxyl-9H-xanthenone is used as starting a material instead of 3,4,6-trimethyl-9H-xanthenone, and as a result, 60mg of yellow solid is obtained, and the yield is 40%; m.p. is 157°C - 158°C; 1 H NMR (300 MHz, $CDCl_3$): 0.81 (s, 3H), 1.24-1.29 (m, 7H), 1.64 (s, 3H), 1.67 (s, 3H), 1.68 (s, 3H), 2.27 (dd, J1 = 13.5Hz, J2 = 4.8Hz, 1H), 2.45-2.49 (m, 3H), 3.33 (d, J=7.2 Hz, 2H), 3.43 (dd, J1= 6.6 Hz, J2= 4.8Hz, 1H), 4.47 (t, J=6.6Hz, 1H), 5.20 (dd, J1= 7.2 Hz, J2= 1.2Hz, 1H), 5.41 (s, 1H), 6.79 (d, J=8.1 Hz, 1H), 7.37 (d, J = 8.1 Hz, 1H), 7.41 (d, J = 6.6 Hz, 1H), IR (KBr): 3416.4, 2969.4, 2909.6, 1739.5, 1654.8, 1607.8, 1448, 1313.7, 1249.2, 1213.7, 1037.7, EI-MS(m/z): 448, 436, 420, 405, 377, 351, 323, 281, Anal. calcd for C28H32O5.CH3OH (%): C 72.08, H 7.35 ; Found: C72.02, H 7.30.

Claims

1. A compound of Formula (I) or a pharmaceutically acceptable salt thereof:

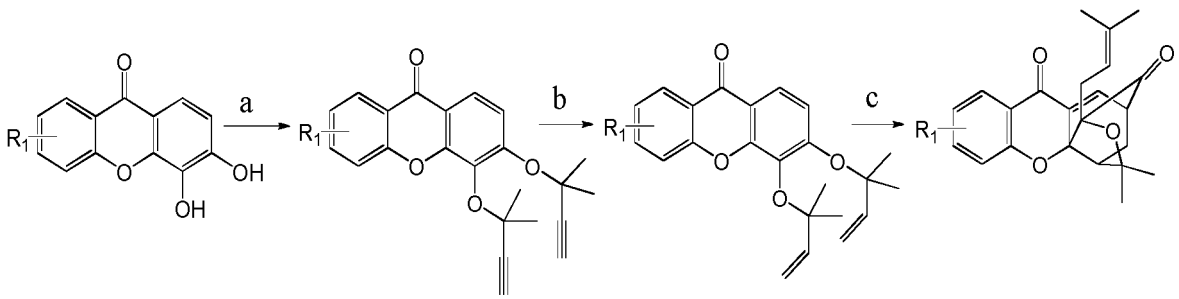


(I)

wherein said compound of Formula (I) carries one or two R_1; when it carries one R_1, R_1 is a hydroxyl group; when it carries two R_1, one of R_1 is a hydroxyl group, and the other R_1 is an isopentenyl roup;
wherein R_2 is hydrogen, halogen, a hydroxyl group, an alkoxy group containing C_1 - C_4 carbons, an amide group containing C_1 - C_4 carbons, a carboxyl group, or an aldehyde group.

2. The compound of Formula (I) or a pharmaceutically acceptable salt thereof according to Claim 1, wherein R_2 is hydrogen, a hydroxyl group, an aldehyde group, a carboxyl group, or an amide group.

3. A preparing method of the compound of Formula (I) according to Claim 1, the method comprises the following preparing steps which are represented below:



wherein R_1 is the same as in Claim 1; and a, b and c are reaction conditions wherein:

a is K_2CO_3, KI, chloro-methyl-butyne, CuI and acetone;
b is 10% $Pd/BaSO_4$ and ethyl acetate; and
c is N,N-dimethyl formamide.

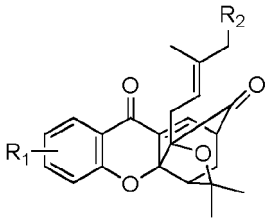
4. A pharmaceutical composition comprising the compound of Formula (I) or a pharmaceutically acceptable salt thereof according to Claim 1 and a pharmaceutically acceptable carrier thereof.

5. Use of the compound of Formula (I) or a pharmaceutically acceptable salt thereof according to Claim 1 for the preparation of anti-tumor drugs.

6. The compound of Formula (I) or a pharmaceutically acceptable salt thereof according to Claim 1, for use as an anti-tumor drug.

Patentansprüche

1. Eine Verbindung der Formel (I) oder ein pharmazeutisch verträgliches Salz davon:

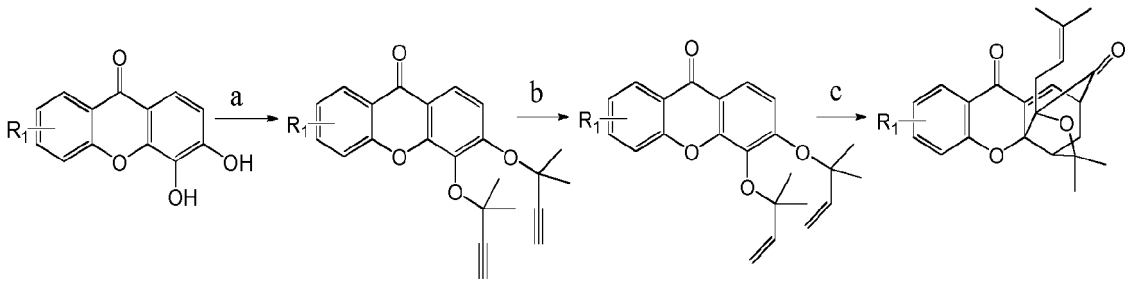


(I)

wobei die Verbindung der Formel (I) einen oder zwei Reste R_1 trägt; wenn sie einen Rest R1 trägt, R_1 eine Hydroxylgruppe ist; wenn sie zwei Reste R_1 trägt, einer von R_1 eine Hydroxylgruppe ist und der andere Rest R_1 ein Isopentenylrest ist;
wobei R_2 Wasserstoff, Halogen, eine Hydroxylgruppe, ein Alkoxyrest, enthaltend C_1-C_4-Kohlenstoffe, ein Amidrest, enthaltend C_1-C_4-Kohlenstoffe, ein Carboxylrest oder ein Aldehydrest ist.

2. Die Verbindung der Formel (I) oder ein pharmazeutisch verträgliches Salz davon nach Anspruch 1, wobei R_2 Wasserstoff, eine Hydroxylgruppe, ein Aldehydrest, ein Carboxylrest oder ein Amidrest ist.

3. Ein Herstellungsverfahren der Verbindung der Formel (I) nach Anspruch 1, wobei das Verfahren die folgenden Herstellungsschritte umfasst, die nachstehend dargestellt sind:



wobei R_1 dasselbe wie in Anspruch 1 ist; und a, b und c Reaktionsbedingungen sind, wobei:

a für K_2CO_3, KI, Chlor-methyl-butin, CuI und Aceton steht;
b für 10% $Pd/BaSO_4$ und Ethylacetat steht; und
c für N,N-Dimethylformamid steht.

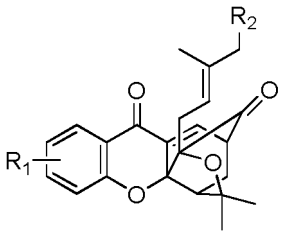
4. Ein Arzneimittel, umfassend die Verbindung der Formel (I) oder ein pharmazeutisch verträgliches Salz davon nach Anspruch 1 und einen pharmazeutisch verträglichen Träger dafür.

5. Verwendung der Verbindung der Formel (I) oder eines pharmazeutisch verträglichen Salzes davon nach Anspruch 1 zur Herstellung von Anti-Tumor-Arzneimitteln.

6. Die Verbindung der Formel (I) oder ein pharmazeutisch verträgliches Salz davon nach Anspruch 1 zur Verwendung als ein Anti-Tumor-Arzneimittel.

Revendications

1. Composé de formule (I) ou sel pharmaceutiquement acceptable de celui-ci :

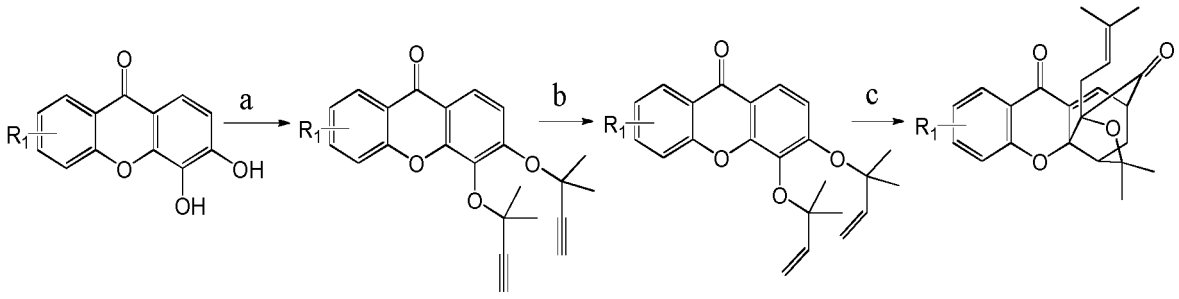


(I)

dans lequel ledit composé de formule (I) porte un ou deux R_1 ; lorsqu'il porte un R_1, R_1 est un groupe hydroxyle ; lorsqu'il porte deux R_1, l'un des R_1 est un groupe hydroxyle, et l'autre R_1 est un groupe isopentényle ;
dans lequel R_2 est l'hydrogène, un halogène, un groupe hydroxyle, un groupe alcoxy contenant des carbones en C_1 - C_4, un groupe amide contenant des carbones en C_1 - C_4, un groupe carboxyle ou un groupe aldéhyde.

2. Composé de formule (I) ou sel pharmaceutiquement acceptable de celui-ci selon la revendication 1, dans lequel R_2 est l'hydrogène, un groupe hydroxyle, un groupe aldéhyde, un groupe carboxyle ou un groupe amide.

3. Procédé de préparation du composé de formule (I) selon la revendication 1, le procédé comprenant les étapes de préparation suivantes qui sont représentées ci-dessous :



dans lesquelles R_1 est le même que dans la revendication 1; et a, b et c sont des conditions de réaction dans lesquelles :

a est K_2CO_3, KI, la chlorométhylbutyne, CuI et l'acétone ;
b est du $Pd/BaSO_4$ à 10 % et l'acétate d'éthyle ; et
c est le N,N-diméthylformamide.

4. Composition pharmaceutique comprenant le composé de formule (I) ou un sel pharmaceutiquement acceptable de celui-ci selon la revendication 1 et un vecteur pharmaceutiquement acceptable de celui-ci.

5. Utilisation du composé de formule (I) ou d'un sel pharmaceutiquement acceptable de celui-ci selon la revendication 1 pour la préparation de médicaments antitumoraux.

6. Composé de formule (I) ou sel pharmaceutiquement acceptable de celui-ci selon la revendication 1, en vue d'une utilisation en tant que médicament antitumoral.

REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

- WO 2008057604 A **[0004]**

Non-patent literature cited in the description

- *Bioorganic & Medicinal Chemistry,* 2008, vol. 16, 4233-4241 **[0003]**